




# Biochemical Parameters in Cognitive Functions

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**Abstract:** Cognitive impairment is a common disease. Many studies attempt to explain the mechanisms of these dysfunctions formation, including correlations between cognitive functions and biochemical parameters. Scientists search for substances that would be indicators of cognitive functions and which could be determined in the cerebrospinal fluid or blood of the subjects. To date, they have isolated a few of such substances; however, research on their specificity, validity and the possibility of their use in diagnostics and prognostic assessment is still ongoing. However, there have been only few reports in the literature systematizing the existing knowledge on this subject, and they are mostly related to Alzheimer's disease, not cognition in general, or referring only to a specific group of substances. This article discusses the most important biochemical exponents of cognitive functions.

**Keywords:** cognitive functions, biochemical markers, neuropsychology

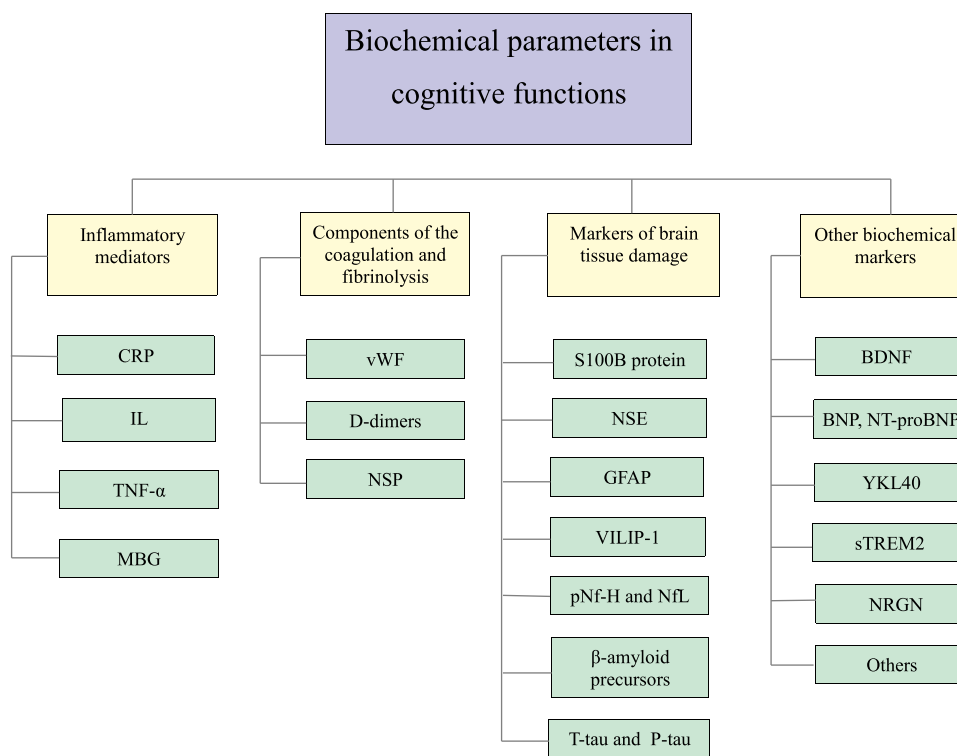
## Introduction

Cognitive dysfunction is an increasingly prevalent condition; incidence rate after age 65 rises exponentially. It is connected with both the physiological aging and various somatic disorders. Numerous studies seek to explain the mechanism of these dysfunctions, including interactions between them and biochemical parameters.

Given the physiology of cognitive functions, it would seem that the best markers for estimating these functions ought to be the neurotransmitters that are engaged in their creation. Impaired cognitive functions are directly related to neurotransmission disorders. Many studies support this intuition.<sup>1,2</sup> However, under physiological conditions, the neurotransmitters in question are produced in nervous tissue, and their level in blood serum or cerebrospinal fluid (CSF) does not always correspond to their level in the brain.<sup>3</sup> Therefore, to appraise their concentration, the rodent, postmortal or special neuroimaging experimentations must be conducted. However, such procedures are costly and hardly accessible. Scientists are thus searching for other substances that would be an indicator of cognitive functions, and be quickly detected in the CSF or blood.<sup>4</sup> Hitherto several substances have been isolated; however, research on their specificity, validity and most importantly usefulness in diagnostics and prognosis are still ongoing. These substances are evaluated usually in subjects after stroke or craniocerebral trauma; less frequently in other disease entities not directly linked to brain damage.<sup>5</sup>

To put it simply, these substances can be divided into four groups<sup>6</sup> (Figure 1): - inflammatory mediators – CRP, IL-1, IL-6, TNF- $\alpha$ , MBG;

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**Figure 1** The most important biochemical parameters in cognitive functions.

**Abbreviations:** CRP, C-reactive protein; IL, interleukins; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; MBG, marinobufagenin; vWF, von Willebrand factor; NSP, neuroseprin; NSE, neuron special enolase; GFAP, glial fibrillary acidic protein; VILIP-1, visinin-like protein 1; pNf-H, phosphorylated neurofilament heavy chain; NFL, neurofilament light chain; T-tau, total tau protein; P-tau, phosphorylated Tau protein; BDNF, brain-derived neurotrophic factor; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of BNP; YKL40, chitinase-3-like protein 1; sTREM2, triggering receptor expressed on myeloid cells 2; NRGN, neurogranin.

- neural tissue markers – S100B protein, NSE, GFAP, pNf-H, Nf-L, VILIP-1, T-tau, P-tau, beta-amyloid precursors;

- components of the coagulation and fibrinolysis systems – vWF, D-dimer, NSP; - others – BDNF, BNP/NT-proBNP, YKL40, sTREM2, NRGN and many others.

## Inflammatory Mediators

Inflammation process is expressed by five features, proposed in ancient times by Celsus and Galen, that include redness, pain, increased warming, swelling and impaired functions. However, developing inflammation does not have to reveal in this fashion. There is a slight grade of subclinical inflammatory response, without the ordinary symptoms detailed above, with activation of the inflammatory cascade and increased biochemical indicators of inflammation.<sup>7</sup> This process is related to age – is more demonstrable in older individuals and is called “inflammaging”. It is also accepted that this process may be associated with the development of illnesses that proceed with inflammation, such as atherosclerosis, diabetes, osteoporosis and Alzheimer’s disease (AD). Launching the anti-

inflammatory response may have a defensive function.<sup>7</sup> Many studies confirm the relationship between inflammation, understood in this way, and the development of many disorders, and – what is more important in this paper – cognitive impairment.<sup>8</sup>

C-reactive protein (CRP) is one of the acute phase proteins, engaged in the body’s immune response. For the wide availability and relatively low costs, with a high sensitivity of signage, it is a broadly used exponent of inflammation in a clinical practice. This protein is synthesized by the liver in response to inflammation. The increased concentration of hs-CRP (CRP determined by the high sensitivity method) is observed in people with obesity, diabetes, increased waist circumference or elevated LDL cholesterol. It is also believed that it plays an important role in the brain aging process, including the development of cognitive disorders.<sup>9–12</sup>

Chinese researchers conducted a meta-analysis of 170 studies comparing the level of various inflammatory exponents, including CRP, in healthy individuals and Alzheimer’s patients. It turned out that among subjects with Alzheimer’s dementia, CRP values were significantly

higher than in healthy ones ( $p < 0.05$ ).<sup>13</sup> Also in many other disease entities, CRP levels correlates with cognitive impairment – in patients with chronic kidney diseases, depression, schizophrenia, bipolar disorder, Parkinson's disease, but also in healthy individuals.<sup>14,15</sup>

Weinstein et al conducted long-term observation of cognitive functions in subjects with chronic ischemic heart disease. They showed that the previously observed higher CRP level was associated with worse cognitive functions assessed several years later.<sup>16</sup> Interesting studies were also carried out by Corlier and companions who, in a 9-year follow-up, evaluated the thickness of the cerebral cortex (measured in several places considered crucial for cognitive functions, inflammation and physical activity) and compared results of these measurements with the level of CRP and metabolic risk factors. According to the hypothesis, people with a higher baseline CRP had significantly thinner cerebral cortex in four regions crucial for the development of Alzheimer's dementia in the 9th year of study. Interestingly, scientists have not observed such a direct link between metabolic risk items and brain structure.<sup>9</sup>

Interleukins (IL) belong to proteins and the cytokines that are involved in the body's immune and hematopoietic processes. They play a role in the communication between white blood cells and originally mainly this role was seen. However, it is now recognized that they also communicate with other types of cells, not just leukocytes. This is a heterogeneous group in terms of structure and function, which is why it is divided into several subgroups. It is considered that IL-6 and IL-1 ( $\alpha$  and  $\beta$ ) are the most significant for acute phase regulation. Proteins from the IL-1 family show activity on almost all types of immunocompetent cells. IL-1 $\beta$  has the ability to pass from peripheral blood through the blood-brain barrier to the brain system. There, by stimulating macrophage-like cells, it induces the production of further interleukins. On the other hand, brain structures (such as the hippocampus) obtain signal through specific receptors for these interleukins. Persistent inflammation may thus modulate brain functions.<sup>17,18</sup> Studies have proved that elevated stage of some interleukins is related with poorer cognitive functioning.<sup>19–21</sup> For instance, levels of IL-6 are raised among patients with dementia and the ones with cognitive deficits in the course of cardiovascular, rheumatic or liver diseases.<sup>22</sup> The increased IL-6 concentration corresponds with the deterioration of memory and the severity of the symptoms of chronic fatigue syndrome.<sup>18,21</sup> Meyers et al

studied patients with acute myeloid leukemia and myelodysplastic syndromes and indicated a negative correlation between IL-6 level and memory, and a positive correlation between IL-8 level and memory.<sup>23</sup>

Italiani and colleagues demonstrated similar relationships for cytokines and receptors in the IL-1 family – they observed elevated levels of both IL-1 $\alpha$  and IL-1 $\beta$  in individuals with AD.<sup>24</sup> Other researchers note the probable importance of these interleukins for the development of cognitive declines in bipolar disorder and after cerebral trauma.<sup>25,26</sup>

Scientific reports on IL-1 function are not consistent. Objective research is providing more and more evidence confirming that IL-1 is essential for memory development. Many publications also confirm their participation in opposite processes – through disturbing the consolidation of memory and hippocampal-dependent memory. An attempt to reconcile these discoveries are the results got by Goshen and colleagues, according to which exogenous IL-1 $\beta$  in low concentrations improves remembrance, but disturbs it in high concentrations. It seems, therefore, that it may take part in both these opposing processes and the effect of its action depends on its concentration.<sup>27</sup>

Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) is a pro-inflammatory cytokine, mainly produced by monocytes and macrophages. Both forms of TNF- $\alpha$  – soluble and anchored – exhibit biological activity. The cells they stimulate produce a broad spectrum of cytokines, triggering a cascade of events both inducing and inhibiting the inflammatory response. This leads to mitochondrial dysfunctions, enhanced oxygen free radical production, increased proapoptotic protein generation (Bax and p53), release of cytochrome c from mitochondria, activation of caspase 3, and induction of apoptosis and cell death. In the clinical course, this may manifest cognitive impairment, especially when the above processes occur in brain cells.<sup>28</sup> Many studies confirm the relationship between TNF- $\alpha$  (or its receptors) and cognitive deterioration in various disease entities.<sup>15,23,28</sup> Increase in TNF-TNFR2 receptor concentration was observed among women receiving chemotherapy for breast cancer, which correlated with memory impairment in these cases.<sup>29</sup> It has also been proven that treatment with TNF- $\alpha$  inhibitors (taken in various disease entities) is associated with the improvement of cognitive and behavioral functions.<sup>30,31</sup>

There are, however, opposite opinions – Polish researchers in a meta-analysis note that subjects with schizophrenia function better cognitively at higher levels of

TNF- $\alpha$ .<sup>14</sup> In the same meta-analysis, they remark that TNF- $\alpha$ , promotes the development of cognitive disorders among patients with bipolar disorder.<sup>14</sup>

Marinobufagenin (MBG) is a relatively new substance that seems to have a high diagnostic potential.<sup>5</sup> It is released due to brain damage during trauma. Its increased concentration is also observed in preeclampsia and eclampsia.<sup>32</sup> It is involved in the initiation and maintenance of the inflammatory response, secondary to increasing the permeability of brain endothelial cells and deterioration of brain functions, including cognitive functions.<sup>33</sup>

## Markers of Brain Tissue Damage

Biomarkers of brain tissue damage may have a glial origin (eg, S100B protein, glial fibrillary acidic protein) or a neuronal origin (eg, tau protein, neuron special enolase). The most important of them are discussed below.

S100B protein is one of the oldest and well-tested biomarkers of brain damage. It occurs in astrocytes and it belongs to the group of calcium-binding proteins, which participate in the regulation of calcium concentration inside the cell.

It was proved that its serum concentration correlates with abnormalities in neuroimaging studies such as size and type of brain damage.<sup>34</sup> It was also observed that it is associated with cognitive impairment, mainly in terms of attention, memory and speed of information processing.<sup>34,35</sup> Many studies confirm its usefulness – eg, in assessing prognosis after carotid surgery, after thrombolysis, resuscitation or coronary artery bypass.<sup>36–39</sup>

On the other side, some studies emphasize the low specificity of this protein and its occurrence outside the central nervous system. This may hinder the interpretation of results and undermine their credibility.<sup>40</sup>

Neuron special enolase (NSE) is an enzyme with glycolytic activity. It occurs mainly in the cytoplasm of nerve cells, but it has also been found in erythrocytes, thrombocytes and endocrine cells. It is scattered into the extracellular space, when the cell is damaged. Its blood concentration after 72 hours since cerebral injury correlates with unfavorable prognosis.<sup>41</sup>

In 2005 Anand and Stead conducted a meta-analysis of 12 studies, which evaluated NSE in patients with a stroke (a total of 594 patients were examined). They noticed a higher NSE level in the patients' serum in comparison to the control group. Nevertheless, it did not correlate with the clinical status of patients; also its relationship with the extent of a stroke was unclear.<sup>42</sup> Moreover, researchers from Harvard Medical School observed that NSE level in patients

undergoing cardiac surgery correlates better with cognitive deficiency than the S100B protein. Similar dependency was also noticed for tau protein which is described below.<sup>43</sup> In addition, NSE level may be elevated in other clinical situations, not directly related to brain damage.<sup>38,39,44</sup>

Glial fibrillary acidic protein (GFAP), similar as the S100B protein, is found in astroglia; it is a part of the astrocyte cytoskeleton. Numerous studies prove that this is a good indicator of brain damage.<sup>45–47</sup> Papa and co-authors noticed that GFAP levels were significantly different in patients after head injuries and in patients after other traumas without head injury.<sup>48</sup> Some studies have shown correlations with distant results after cerebral trauma, but reports in this case are not consistent.<sup>46,49</sup> Results of many studies pointed out that GFAP is a superior marker to others (in terms of correlation with imaging studies, with cognitive functions or assessment of prognosis).<sup>49,50</sup> Herrmann et al compared results of biochemical tests (of protein S100B and GFAP) with results of neuroimaging tests and clinical condition after strokes at the time of admission to hospitals and during four following days of hospitalization.<sup>50</sup> It turned out that the constellation of these proteins' levels correlated with stroke type and prognosis. Particularly characteristic was the system of proteins in lacunar stroke, in which high GFAP levels were observed at the time of admission to hospital with its gradual decrease to the physiological level on the second day. Such dynamic of changes was associated with better prognosis. GFAP turned out to be a very sensitive marker, especially at small cerebral infarcts.<sup>50</sup>

Phosphorylated neurofilament heavy chain (pNf-H) and neurofilament light chain (NfL) are components of neurofilaments – specific proteins in the cytoskeleton of neurons, found mainly in myelinated axons. They are released into the CSF and then into the blood during axon damage. Their concentration in CSF is elevated after brain injury.<sup>51,52</sup> In studies conducted among children, who experienced brain traumas, the level of Nf-H correlated with the severity of brain damage and distant results.<sup>53</sup> Its elevated levels are also observed in patients undergoing chemotherapy for breast cancer or in post-operative delirium.<sup>54,55</sup> Research to date suggests that also plasma NfL may be a good biomarker of cognitive function in patients with AD and in people with Parkinson's disease and other neurological disorders.<sup>51,56,57</sup>

Visinin-like protein 1 (VILIP-1) belongs to a group of neuronal calcium sensors and it is a marker of cognitive

deterioration. Previously, it was only evaluated in the CSF, but recently it is also tested in blood serum.<sup>58</sup> It has also been proven to affect AD, what is probably associated with impaired calcium homeostasis and apolipoprotein E in CSF.<sup>59,60</sup> This exact mechanism was described by Polish researchers who noticed that VILIP-1 affects intercellular neuronal signaling pathways in the central nervous system (cyclic nucleotide cascades and nicotinic signaling), leading to neuronal loss.<sup>61</sup> Its increased concentration is observed among others, after ischemic stroke and after cerebral trauma.<sup>58</sup>

Tau Protein (T-tau and P-tau) is an axonal stabilizing microtubule protein found in both the brain and the spinal cord.<sup>62</sup> Its phosphorylation is crucial in regulating tau function at different neuronal locations, eg, stability of the neuronal cytoskeleton, axonal transport or cell signaling.<sup>63</sup> However, excessive phosphorylation of tau protein is associated with neuron death and it occurs in neurodegenerative diseases, postoperative cognitive impairment, cerebral trauma, and cerebral ischemia.<sup>62</sup> Therefore, total tau (T-tau) in CSF is thought to be a general marker of axonal damage in the brain tissue. Phosphorylated tau (P-tau) then is suggested to be a more specific marker for neurodegenerative tauopathies, including AD.<sup>64</sup>

T-tau in CSF is also a prognostic factor for increased intracranial pressure and clinical status of patients after cerebral trauma.<sup>65</sup> While the level of t-tau in the blood after cerebral injury was significantly increased, it did not correlate with the clinical state.<sup>65</sup>

Beta-amyloid precursors. Beta-amyloid is a well-known component of amyloid plaques, found in AD. It has been noticed that also after craniocerebral trauma there is a rapid increase in the amount of amyloid plaques in the brain. It has also been proven that such trauma is a risk factor for AD. It is believed that it is probably associated with impaired beta-amyloid catabolism and an increase in the concentration of its precursors.<sup>66</sup> Until recently, beta-amyloid assessment was only possible using specialized neuroimaging methods (positron emission tomography) or assessment of its concentration in the CSF. Latest reports indicate the isolation of beta-amyloid precursors from blood (APP)<sub>669–711</sub>/amyloid- $\beta$  (A $\beta$ )<sub>1–42</sub> and A $\beta$ <sub>1–40</sub>/A $\beta$ <sub>1–42</sub>). It was estimated that their level correlates with the concentration of beta-amyloid in CSF and in neuroimaging studies.<sup>67</sup> It should be emphasized that the plasma level of amyloid- $\beta$  strongly correlates with the risk of developing dementia.<sup>57</sup>

## Components of the Coagulation and Fibrinolysis Systems

The von Willebrand factor (vWF) is a plasma glycoprotein involved in the process of primary as well as secondary hemostasis. It is responsible for protecting factor VIII from degradation by forming a complex with it; also allowing platelets to adhere to the collagen at the place of damage. Moreover, research has shown that VWF is involved in the pathogenesis of an early brain damage after an injury.<sup>68</sup> Higher levels of vWF are also observed in patients with ischemic stroke than in the control group. Such a dependency was observed in the acute phase of stroke and three months after the episode.<sup>69</sup> VWF concentration also correlates with cognitive functions and untimely death of patients.<sup>70,71</sup>

D-dimers are fibrin degradation products. It has been proven that their higher concentration correlates with cognitive deterioration and with an increased risk of stroke and cardiovascular events.<sup>70,72</sup> However, it should be emphasized, that it is a marker with very low specificity. That is why possibilities of its use in research and diagnostics are limited. Increased levels of D-dimers are observed, among others, in venous thromboembolism, intravascular coagulation syndrome, after injuries and operations, in stroke, inflammation, cancer, pregnancy, coronary artery disease, atrial fibrillation and aortic diseases.<sup>73</sup>

Neuroseprin (NSP) is an inhibitor of tissue plasminogen activator. It participates in brain development and plays a neuroprotective role.<sup>74</sup> Although this is a relatively new marker of brain damage, and its meaning is not fully known, research using it seems to be promising. During brain damage in the course of ischemic stroke, its level is higher than among the subjects from the control group. Moreover, it was proved that the higher concentration of this neuroprotective marker was, the better the long-term results were obtained.<sup>75</sup> Its elevated level was also observed by Polish researchers among patients after cardiac surgery, what may be related to perioperative brain damage that occurs during such procedures.<sup>5</sup>

## Other Biochemical Markers

Brain-derived neurotrophic factor (BDNF) is a protein belonging to the group of neurotrophins – their role is to regulate short term and prolonged potentials, which stimulate and inhibit various regions of the brain, thus affect the creation of long-term memory.<sup>76</sup> BDNF is a strong

**Table 1** The Most Important Biomarkers of Cognitive Performance, Their Functions and Relation to Cognitive Functions

	<b>Biochemical Marker</b>	<b>Functions</b>	<b>Relation to Cognitive Functions</b>	<b>References</b>
Inflammatory mediators	CRP	Acute phase protein, engaged in the immune response	significantly higher level in patients with AD; correlates with cognitive impairment in many diseases entities and in healthy individuals; correspond with data from neuroimaging studies;	[9–16]
	Interleukins (IL-6, IL-8, IL-1 $\alpha$ , IL-1 $\beta$ )	Mediators involved in immune and hematopoietic processes	increased IL-6 concentration was observed among patients with dementia and the ones with cognitive deficits in other diseases; corresponds with the deterioration of memory; the IL-1 family - essential for memory development, but also participates in opposite processes, increased levels of both IL-1 $\alpha$ and IL-1 $\beta$ in people with AD; positive correlation between the level of IL-8 and memory in some other diseases;	[18–24,27]
	TNF- $\alpha$	Induction of apoptosis and cell death	concentration of both TNF receptors is significantly higher in patients with AD; the increase in TNF-TNFR2 receptor concentration correlates with memory impairment in women treated for breast cancer; treatment with TNF- $\alpha$ inhibitors is associated with the improvement of cognitive and behavioral functions;	[13,28–31]
	MBG	Endogenous cardiotoxic steroid, involved in the inflammatory response	released due to brain trauma; also in preeclampsia and eclampsia; correspond to increased permeability of brain endothelial cells and deterioration of brain function, including cognitive functions;	[32,33]
Markers of brain tissue damage	S100B protein	Calcium-binding protein, that regulates cellular processes	a valid measure of the presence and severity of traumatic brain injury within the first hours after minor head injury, and also after selected surgical procedures; associated with cognitive impairment, mainly in the field of attention, memory and speed of information processing; correlates with abnormalities in neuroimaging studies; low specificity;	[34–37,39–41]
	NSE	Enzyme with glycolytic activity, tumor marker	occurs mainly in the cytoplasm of nerve cells, scattered into the extracellular space when the cell is damaged; its blood concentration after 72 hours since cerebral injury correlates with unfavorable prognosis; in patients undergoing heart surgery correlates with cognitive dysfunction; may be elevated in other clinical situations; moderately associated with AD;	[4,38,39,41–44]

(Continued)

Table I (Continued).

	Biochemical Marker	Functions	Relation to Cognitive Functions	References
	GFAP	Part of the astrocyte cytoskeleton	good indicator of brain damage, marked after trauma or stroke; correlate with imaging tests, cognitive functions, and prognosis;	[45–50]
	pNf-H, Nf-L	Components of neurofilaments	released into the cerebrospinal fluid and then into the blood during axon damage; correlate with cognitive functions; pNf-H is a predictive marker of chemotherapy-induced cognitive impairment; are elevated in cerebrospinal fluid after brain injury and neurological diseases; strongly associated with AD;	[4,51–57]
	VILIP-1	Neuronal calcium sensor; affects intercellular neuronal signaling pathways in the central nervous system	marker of cognitive deterioration; its increased concentration is observed, among others, after ischemic stroke and after cerebral trauma; moderately associated with AD;	[4,58–61]
	P-Tau, T-tau	Axonal stabilizing microtubule protein	it occurs in neurodegenerative diseases, postoperative cognitive impairment, cerebral trauma, and cerebral ischemia; the level of tau protein in cerebrospinal fluid is strongly associated with AD, is a prognostic factor for increased intracranial pressure and clinical status of patients after cerebral trauma; while the level in the blood did not correlate with the clinical state;	[4,62]
	$\beta$ -amyloid precursors	Component of amyloid plaques	can be isolated from blood; their level correlates with the concentration of beta-amyloid in cerebrospinal fluid and in neuroimaging studies; strongly associated with AD;	[4,57,66,67]
Components of the coagulation and fibrinolysis systems	vWF	Plasma glycoprotein involved in haemostasis	vWF concentration correlates with cognitive functions and vascular dementia; also with untimely death of patients; low specificity;	[68–71]
	D-dimers	Fibrin degradation products	higher concentration correlates with cognitive deterioration and vascular dementia; also with an increased risk of stroke and cardiovascular events; low specificity;	[70–73]
	NSP	An inhibitor of tissue plasminogen activator	participates in brain development and plays a neuroprotective role; elevated level after stroke, the higher concentration was, the better the long-term results were obtained;	[5,74,75]

(Continued)

**Table 1** (Continued).

	Biochemical Marker	Functions	Relation to Cognitive Functions	References
Other biochemical markers	BDNF	Strong modulator of synaptic transmission, participates in the processes of maturation, differentiation and apoptosis of nerve cells	plays a role in the long-term potentiation of the hippocampus - learning and memory processes; influence on the formation of long-term memory; deficiencies in BDNF signaling contribute to the pathogenesis of depression and AD;	[76–79]
	BNP, NT-proBNP	Natriuretic peptide, used to diagnose heart failure	the level of NT-proBNP correlate with cognitive functions also in the remote observation; low specificity;	[82,83]
	YKL40	Glycoprotein	moderately correlated with neuroinflammation in AD;	[4,59,84]
	sTREM2	Transmembrane receptor expressed on myeloid cells 2	reflects with the increased risk of AD; may play a role in the pathogenesis of other neurodegenerative diseases	[85]
	NRGN	Protein involved in synaptic plasticity and long-term potentiation	good biomarker of AD, even in the pre-symptomatic phase, serving as a predictive and monitoring marker of Alzheimer's specific cognitive decline	[86,87]

**Abbreviations:** CRP, C-reactive protein; IL, interleukins; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; MBG, marinobufagenin; NSE, neuron special enolase; GFAP, glial fibrillary acidic protein; pNf-H, phosphorylated neurofilament heavy chain; NfL, neurofilament light chain; VILIP-1, visinin-like protein 1; T-tau, total tau protein; P-tau, phosphorylated tau protein; vWF, von Willebrand factor; NSP, neuroseprin; BDNF, brain-derived neurotrophic factor; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of its prohormone, BNP; YKL40, chitinase-3-like protein 1; sTREM2, triggering receptor expressed on myeloid cells 2; NRGN, neurogranin; AD, Alzheimer disease.

modulator of synaptic transmission, it also participates in the processes of maturation, differentiation and apoptosis of nerve cells, contributing to the formation of the central nervous system in embryogenesis and the plasticity of synaptic connections in the mature brain.<sup>77,78</sup> Numerous studies prove that BDNF plays a key role in the long-term potentiation of the hippocampus (LTP), which underlies learning and memory processes.<sup>79</sup> In animal tests, BDNF has been shown to have neuroprotective effects in subjects after ischemic-hypoxic episodes. It has also been proven that deficiencies in BDNF signaling contribute to the pathogenesis of many different diseases and disorders, such as depression and AD.<sup>79</sup>

Brain natriuretic peptide is a protein belonging to natriuretic peptides. There are also atrial natriuretic peptide (ANP) and natriuretic peptides type C and D (CNP, DNP). NT-proBNP is the N-terminal fragment of its prohormone – BNP. In clinical practice, they are routinely used to diagnose heart failure. They are produced, among others, by cardiomyocytes, in response to an increase in their tension caused by increased preload or afterload. They cause the increase of diuresis and natriuresis, have sympatholytic activity, inhibit the RAA system and also

reduce the activity of baroreceptors. All of these activities lead to the reduction of blood pressure and the reduction of pre- and afterload of the ventricles. BNP and NT-proBNP are also thought to be sensitive indicators of brain damage that may be useful in clinical assessment, prognosis, and risk of death after stroke. It has been shown that increased BNP plasma levels in patients after a stroke incident can predict mortality with sensitivity and specificity close to 75%.<sup>80</sup> In another analysis, the specificity and sensitivity in predicting death were 88.9% and 98.2%.<sup>81</sup> Interesting studies on a large population were carried out by German scientists. They examined 419 patients with mild cognitive impairment and 1206 people without cognitive impairment and they correlated cognitive testing results with NT-proBNP levels. It turned out that cognitive functions correlated, regardless of other factors, with the level of this marker.<sup>82</sup> A similar relationship in the five-year observation of patients after 85 years of age was observed by Dutch scientists.<sup>83</sup>

## Discussion

The most relevant information, summarizing this article, is outlined in [Table 1](#).



It should be emphasized that the content of the article, based on numerous citations, indicates little significant clinical and scientific usefulness of factors from groups of inflammatory mediators and coagulation/fibrinolysis components. Testing the level of markers of nerve tissue damage, in particular Tau Protein (T-tau and P-tau), is much more valuable. The existing evidence, in line with the current biochemical research on the basis of cognitive impairment, concerns many parameters. However, research using biochemical markers in diseases with accompanying cognitive dysfunctions other than Alzheimer's dementia seems to be particularly promising.

However, it should be also emphasized that in this report we have not exhausted the topic of biochemical parameters of cognitive functions. There are more substances that should be pointed out for completeness. These include chitinase-3-like protein 1 (YKL-40), a glycoprotein correlated with neuroinflammation in AD.<sup>59,84</sup> Another marker, triggering receptor expressed on myeloid cells 2 (sTREM2) reflects with increased risk of AD and also may play a role in the pathogenesis of other neurodegenerative diseases.<sup>85</sup> Neurogranin (NRGN) is a postsynaptic protein involved in synaptic plasticity and long-term potentiation. It appears to be a good biomarker of AD, even in the pre-symptomatic phase, serving as a predictive and monitoring marker of Alzheimer's cognitive decline.<sup>86,87</sup> Besides, new reports on this issue still appear.<sup>88,89</sup>

## Conclusion

In summary, more and more, is known about substances that correlate with cognitive dysfunctions. Despite this, there is a lack of convincing data indicating the clear association of any substance with the assessment of cognitive functions that would be sensitive and specific enough to be able to use it in practice. Further research is needed to deepen existing knowledge on this subject.

## Disclosure

The authors report no conflicts of interest for this work.

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